The question of measuring blood cholesterol values for assessing risk in individuals will continue to be debated. What is certain is that blood cholesterol concentrations in British men are high and constitute a considerable risk for ischaemic heart disease. The high risk approach in the United States and Great Britain would appear to have severe limitations. Given the present distribution of blood cholesterol concentrations in British men, nothing short of a population approach is likely to be effective, and even that would have to be applied from childhood if it is to have much effect.

A G SHAPER
STUART J POCOCK

Department of Clinical Epidemiology and General Practice,
Royal Free Hospital School of Medicine,
London NW3 2PF

1 Anonymous. Consensus conference: lowering blood cholesterol to prevent heart disease. *JAMA* 1985;**253**:2080-6.
2 Rahimtoola SH. Cholesterol and coronary heart disease: a perspective. *JAMA* 1985;**253**:2094-5.
3 The Lipid Research Clinics. *Population studies data book*. Vol 1. *The prevalence study*. Bethesda, Md: NIH, 1980. (Publication No 80-1527.)
4 Thelle D, Shaper AG, Whitehead TP, *et al*. Blood lipids in middle-aged British men. *Br Heart J* 1983;**49**:205-13.
5 Ritchie CD, Bailey A. Hypercholesterolaemia and coronary heart disease: an answer. *Br Med J* 1984;**288**:862.
6 Oliver MF. Strategies for preventing and screening for coronary heart disease. *Br Heart J* 1985;**54**:1-5.
7 Shaper AG, Pocock SJ, Walker M, *et al*. Risk factors for ischaemic heart disease: the prospective phase of the British regional heart study. *J Epidemiol Community Health* (in press).

Co-trimoxazole toxicity

SIR,—The Committee on Safety of Medicines has recently circulated doctors with information on deaths associated with the use of co-trimoxazole (trimethoprim and sulphamethoxazole) and trimethoprim alone. In it the committee states that it would be unwise at this stage to assume that trimethoprim is substantially less liable to cause fatal adverse reactions than co-trimoxazole. No discussion is given to the well known toxicity and fatalities associated with sulphonamides. This is regrettable since most of the deaths associated with the use of co-trimoxazole are typical of sulphonamide toxicity—blood dyscrasias (50 deaths) and skin reactions (14). When sulphonamides are used alone about one case of Stevens-Johnson syndrome occurs per million prescriptions[1] and the incidence of agranulocytosis is about 0·1-0·3%,[1-3] although not all of the latter cases are fatal. Furthermore, clinical trials have shown that other toxic reactions are commoner with co-trimoxazole than with trimethoprim.[4-6] In vitro, human and murine haematopoiesis is inhibited to a greater extent by co-trimoxazole than by either trimethoprim or sulphamethoxazole.[7]

The question of differential toxicity between co-trimoxazole and trimethoprim is now an important issue since the preparation is widely prescribed and many clinical studies suggest that all the antibacterial activity of co-trimoxazole in vivo results from only the trimethoprim component.[8-10] A recent study could not identify any sulphamethoxazole in sputum or saliva during or after a course of co-trimoxazole.[11] So far as we are aware none of the many comparative trials in urinary and respiratory infections that have been performed have provided convincing evidence that the addition of sulphamethoxazole to trimethoprim is of benefit. Moreover, if a patient does develop a toxic reaction after co-trimoxazole it is unwise to prescribe either of the component drugs on subsequent occasions. Speculation that the sulphonamide component of co-trimoxazole protects against selection of resistance has not been supported by clinical studies.[12,13]

From the data presented by the CSM an immediate withdrawal of the drug in the elderly seems warranted, and we would urge the CSM to consider removing the product licence for many other indications. Trimethoprim and a sulphonamide may still be indicated for certain specific conditions—for example, in the management of *Pneumocystis carinii* infection. If so, then surely the selection of a sulphonamide and its dose should be made independently of the trimethoprim moiety, based on the particular patient, notably his renal function? Co-trimoxazole may still occasionally be useful in sexually transmitted diseases and could be prescribed by the appropriate specialists.

We believe that the CSM has not presented us with an accurate appraisal of the information. It would seem reasonable to expect greater toxicity from the combination of two dissimilar drugs than either single agent.

R W LACEY
P M HAWKEY
S K DEVARAJ
M R MILLAR
T J J INGLIS
P G R GODWIN

Department of Microbiology,
University of Leeds,
Leeds LS2 9JT

1 Anonymous. To-day's drugs: sulphonamides. *Br Med J* 1968;i: 674-6.
2 Goodman LS, Gilman A. *The pharmacological basis of therapeutics*. New York: Macmillan, 1955:1298.
3 Yow EM. A re-evaluation of sulfonamide therapy. *Ann Intern Med* 1955;**43**:323-44.
4 Kasanen A, Anttila M, Elfving K, *et al*. Trimethoprim pharmacology, antimicrobial activity and clinical use in urinary tract infections. *Ann Clin Res* 1978;**10**(suppl 22):1-39.
5 Koch UJ, Schumann KP, Küchler R, Kewitz H. Efficacy of trimethoprim, sulphamethoxazole and the combination of both in acute urinary tract infection. Clinical and pharmacokinetical studies. *Chemotherapy* 1973;**19**:314-21.
6 Brumfitt W, Pursell R. Double-blind trial to compare ampicillin, cephalexin, co-trimoxazole and trimethoprim in treatment of urinary infection. *Br Med J* 1972;ii:673-6.
7 Golde DW, Bersch M, Quan SG. Trimethoprim and sulphamethoxazole inhibition of haematopoiesis in vitro. *Br J Haematol* 1978;**40**:363-7.
8 McKendrick MW, Geddes AM, Farrell ID. Trimethoprim in enteric fever. *Br Med J* 1981;**282**:364-5.
9 Trimethoprim Study Group. Comparison of trimethoprim at three dosage levels with co-trimoxazole in the treatment of acute symptomatic urinary tract infection in general practice. *J Antimicrob Chemother* 1981;**7**:179-83.
10 Mabeck CE, Vejlsgaard R. Treatment of urinary tract infections in general practice with sulphamethizole, trimethoprim or co-trimazine (sulphadiazine-trimethoprim). *J Antimicrob Chemother* 1980;**6**:701-8.
11 Brumfitt W, Hamilton-Miller JMT, Havard CW, Tansley H. Trimethoprim alone compared to co-trimoxazole in lower respiratory infections: pharmacokinetics and clinical effectiveness. *Scand J Infect Dis* 1985;**17**:99-105.
12 Lacey RW. Do sulphonamide-trimethoprim combinations select less resistance to trimethoprim than the use of trimethoprim alone? *J Med Microbiol* 1982;**15**:403-27.
13 Stamm WE, Counts GW, Wagner KF, *et al*. Antimicrobial prophylaxis of recurrent urinary tract infections; a double-blind, placebo controlled trial. *Ann Intern Med* 1980;**92**: 770-5.

A somatic component to myocardial infarction

SIR,—I was interested to read the report by Professor Alexander S Nicholas and others (6 July, p 13) describing palpable paravertebral soft tissue changes in patients recovering from acute myocardial infarctions. They conclude that the observed palpable soft tissue changes are specific to patients recovering from acute myocardial infarction. They further claim that these changes may help in diagnosing infarction or in predicting an impending infarction. I see no justification for such conclusions. The paper appears to have several major flaws. The control and study groups were not matched in many important ways and this means that no conclusions can be drawn from the observed differences.

The study group comprised 25 patients recovering from an acute myocardial infarction who were examined within three to five days of the event. The control group included eight (36%) normal volunteers and only six (27%) who were conceivably acutely ill (one patient each with pneumonia, subarachnoid haemorrhage, cholecystitis, thrombophlebitis, pancreatitis, and pulmonary abscess). The difference between the number of acutely ill patients in each group was highly significant ($p<0·0001$ exact test) and important. When ill patients are confined to bed, as they would be after acute myocardial infarction, skin blood flow changes, as does underlying skin nutrition, especially in areas of pressure—for example, heels, buttocks, and thoracic spine. This results in erythema and eventually skin loss. Early changes may possibly be felt as "skin warmth" and "firmness." Ambulant patients would not be expected to have such changes.

Acute myocardial infarction is a dramatic and painful event and is associated with increased sympathetic activity. It is feasible that such activity may have somatic manifestations. Indeed the concept of somatisation of anxiety mediated by the autonomic nervous system is not new—for example, tension headache, irritable bowel syndrome. Few of the control group were acutely ill and so they were unlikely to have increased sympathetic drive or any somatic changes associated with this.

The authors believe that their observed palpable changes are mediated by the autonomic nervous system. Many drugs interfere with the autonomic nervous system, and again the control and study groups differ. More patients in the control group were taking hypnotics and tranquillisers ($p=0·001$ exact). More patients in the study group were taking diuretics, which may change skin turgor ($p<0·01$ exact), and antianginal drugs ($p<0·0001$ exact). β Adrenergic blockers modulate autonomic nervous responses and decrease skin blood flow. Nitrates and calcium channel blockers are vasodilators and increase skin blood flow and are often associated with oedema and flushing. The palpable changes observed in the study group might have been caused by their medication.

K S CHANNER

Bristol Royal Infirmary,
Bristol BS2 8HW

SIR,—Professor Alexander S Nicholas and his colleagues (6 July, p 13) make some extravagant claims about the information obtained from palpating the thoracic paravertebral soft tissues. While they appear to acknowledge that any changes in consistency of such tissues may reflect alterations in sympathetic tone, which may well be increased after myocardial infarction, they do not make any comment about the number of their patients receiving antianginal preparations who were receiving β blockers. Nor do they comment on whether this group are palpably different from those not receiving β blockers.

One presumes that patients recovering from acute myocardial infarction in an intensive care unit will have been bedfast for the first 48-72 hours and thus pressure effects on the paravertebral tissues must contribute significantly to the authors' findings. I have grave doubts about extrapolating this sort of work to previously ambulant patients presenting with suspected myocardial infarction. Also I have reservations about their control group, most of whom appeared to have conditions which would not prevent them being ambulant; indeed eight were not inpatients.

Finally, I have yet to see any dog that rests on its back and therefore doubt that much can be inferred about soft tissue changes in the human paravertebral area from a canine model.

DUNCAN R FORSYTH

Department of Medicine,
Bristol Royal Infirmary,
Bristol BS2 8HW

** The authors reply below.—ED, *BMJ*.